REMARKS

A check including: (a) the fee for a three month extension of time, four added dependent claims and one added independent claim; and (b) the fee for filing an Information Disclosure Statement accompanies this response. Any additional fees that may be due in connection with filing this paper or with this application during its pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050. An Information Disclosure Statement accompanies this response. Also attached to this response is an Appendix providing certified English translations of the following two Japanese priority applications of the above-captioned application: (1) JP 9-260972, titled "Transporter Genes," filed September 8, 1997; and (2) JP 10-156660, titled "Transporter Genes," filed May 20, 1998.

Amendments to the Specification

The title of the application has been amended to reflect the subject matter of the claims, as suggested by the Examiner. The specification at page 17, lines 5-6, has been amended to identify the amino acid sequences disclosed in Figure 3, thereby complying with the requirements of the Sequence Rules and addressing the objection raised by the Examiner. Basis for the amendment can be found in the Sequence Listing as originally filed, which lists "SEQ ID NO:1" as the identifier for the OCTN1 amino acid sequence set forth in Figure 3, and "SEQ ID NO:3" as the identifier for the OCTN2 amino acid sequence set forth in Figure 3. No new matter is added.

Amendments to the Claims

Upon entry of the above amendment, claims 8-11, 13, 16-27 and 29-36 will be pending in this application. Solely in the interest of advancing prosecution, Claims 12, 14 and 15 are cancelled herein. Applicant reserves the right to file continuation and/or divisional applications directed to any cancelled and/or unclaimed subject matter.

Claim 10 is amended herein to specify a range of conservative amino acid substitutions from one to 30 amino acid substitutions. Basis for amended Claim 10 can be found in the specification, for example, at page 5, lines 9-16. Claim 11 is amended herein to clarify its subject matter by specifying conditions under which the claimed isolated nucleic acid hybridizes to a probe, and the sequence of the probe. Claim 11 as amended herein also

incorporates the limitations of claim 12, which is cancelled herein; the dependencies of Claims 13, 20 and 25 are amended accordingly. Basis for amended Claim 11 can be found in the specification, for example, at page 10, line 13 to page 11, line 4. No new matter is added.

New claims 29-36 are added herein. Basis for the added claims can be found in the specification, for example, at page 5, lines 23-25; page 6, lines 11-14; page 10, lines 4-6; page 10, line 13 to page 11, line 4; page 12, lines 7-14; page 12, line 20 to page 13, line 14; page 14, line 18 to page 16, line 25; and Examples 6-8. No new matter is added.

I. SEQUENCE COMPLIANCE

The Examiner objects that the application fails to comply with the Sequence Rules (37 C.F.R. 1.821-1.825). Specifically, it is alleged that the sequences disclosed in Figure 3 are not accompanied by references to their corresponding sequence identifiers. In response, the specification is amended herein at page 17, lines 5-6, to identify the sequence identifiers for the sequences set forth in Figure 3. As described under "Remarks" above, no new matter is added. Applicant respectfully submits that the rejection is obviated by virtue of this amendment.

II. OBJECTIONS TO THE SPECIFICATION

1) Embedded hyperlink: The Examiner objects that the embedded hyperlink at page 12, line 20, is contrary to policy as set forth in MPEP § 608.01 and must be deleted. The specification is amended herein to remove the embedded hyperlink

2) Title: The Examiner objects that the title is not clearly indicative of the subject matter of the claims and therefore is not descriptive. This objection is addressed herein by replacing the previous title with a new title, "POLYNUCLEOTIDES ENCODING hOCTN1 POLYPEPTIDE," as suggested by the Examiner.

III. THE REJECTION OF CLAIMS 8-25 AND 27 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 12, 20 and 25 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, it is alleged that the claims are indefinite because they specify that the nucleic acid of Claim 11 encodes a polypeptide that is a transporter of an organic cation, yet Claim 11 recites a nucleic acid that is a complement of SEQ ID NO:2. The Examiner states that it is unclear how the complement of SEQ ID NO:2 can encode a polypeptide that is a transporter of an organic cation.

This rejection is rendered moot with respect to Claim 12, which is cancelled herein. With respect to Claims 20 and 25, Applicant has amended Claim 11, on which these claims depend, to clarify that the isolated nucleic acid hybridizes to a probe, and it is the probe whose sequence is the complement of the sequence set forth in SEQ ID NO:2. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

IV. THE REJECTION OF CLAIMS 8-25 AND 27 UNDER 35 U.S.C. §101 - UTILITY

Claims 8-25 and 27 are rejected under 35 U.S.C. §101 as allegedly lacking a credible, substantial and specific utility because they are novel biological molecules and "must undergo extensive experimentation" before the utility can be well established. In particular, it is alleged that the OCTN1 transporter polypeptide clearly is an "orphan protein" because, according to the Examiner, the specification merely identifies the polypeptide and does not provide any methods or working examples that indicate a physiological significance, such as a biological activity, phenotype, disease or condition, binding partner or other specific feature that is disclosed as being associated with OCTN1.

The Examiner goes on to say that none of the uses asserted by Applicant in the specification as patentable utilities are substantial or credible. The Examiner points to the following uses cited in the specification: (1) to design drugs that would improve transport and absorbability mediated by the transporter; (2) for gene therapy; (3) to develop carcinostatics that would be readily absorbed by the transporter; and (4) to design an antisense DNA oligonucleotide and alleges that these utilities are not specific because they can be performed "with any polypeptide and nucleic acid," nor are they substantial because they are "not presented in mature form." The Examiner alleges that the instant situation is analogous to the facts of Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct. 1966), in which a novel compound described as potentially useful as an anti-tumor agent did not evidence nor establish real world utility.

This rejection is respectfully traversed. The rejection is rendered moot with respect to Claims 12, 14 and 15, which are cancelled herein.

As discussed below, Applicant respectfully submits that the Examiner has failed to apply the proper standard for establishing whether a utility taught in the specification is credible, specific and substantial. Only one such utility need be asserted, and the instant application goes far beyond that minimum requirement.

The instant specification asserts at least one credible, specific and substantial utility

Independent claim 8 is directed to isolated nucleic acids encoding polypeptides that are at least 70% homologous to the polypeptide having the amino acid sequence set forth in SEQ ID NO:1. Claim 9 is directed to an isolated nucleic acid encoding a polypeptide comprising the sequence of SEQ ID NO:1, and new claim 36 is directed to an isolated nucleic acid encoding a polypeptide consisting of the sequence of SEQ ID NO:1. Claim 11 specifies isolated nucleic acids that hybridize to a probe having a sequence complementary to SEQ ID NO:2 under particular conditions of high stringency. Dependent claims specify nucleic acids encoding polypeptides of higher percent homologies (76%, at least 80%, at least 90%), expression vectors and cultured cells containing the nucleic acids, methods of producing the encoded polypeptides from the cultured cells, and methods of screening for compounds, including carcinostatic compounds, that are transported by polypeptides encoded by the isolated nucleic acids. Dependent claim 13 specifies that the isolated nucleic acid of claim 11 encodes the polypeptide having the amino acid sequence set forth in SEQ ID NO:1.

The specification teaches that the claimed nucleic acids encode heretofore unknown polypeptides that are identical to or at least 70% homologous to the sequence of amino acids set forth in SEQ ID NO:1. The specification notes that these previously unknown polypeptides are presumed to function as organic cation transporter proteins, based on the homology of OCTN1 to known organic cation transporters. The specification further teaches that OCTN1, and related family members including human OCTN2 and their corresponding genes in mice, in fact do contain the structural features of a cation transporter, including several transmembrane domains, a transporter consensus sequence motif, and a nucleoside binding domain. The specification then goes on to demonstrate in numerous working examples that, not only do these proteins contain the features of an organic cation transporter as extensively studied and characterized in the instant application, but they in fact do function as cation transporter proteins in cells. The specification also describes an extensive study of the distribution of these proteins in a variety of cells and tissues, including their prevalence in tumor cell lines. The specification demonstrates, in several working examples (*see*, for example, Examples 6-8), that OCTN1 and OCTN2 transport a variety of organic cations, including TEA, carnitine, mepyramine and quinidine, and several carcinostatic compounds including actinomycin D, etoposide, vinblastine and daunomycin.

Thus, the specification clearly and extensively characterizes the structural features and biological activity of the newly discovered gene family. The teachings of the specification establish that this new gene family belongs to the general class of organic cation transporter proteins, several of which were known and studied in biological systems. Based on the properties of these newly discovered genes, Applicant has gone on to assert utilities that are specific, substantial and credible, as discussed below.

Specific

Applicants have asserted not one, but several specific utilities in the specification. The Examiner alleges that no specific utility is provided because the experiments can be performed "with any polypeptide and nucleic acid." To the contrary, the asserted utilities are specific because Applicant has not merely hypothesized that the claimed nucleic acids and their encoded proteins "may be useful" in a general sense. See MPEP §2107.01. Rather, the specification teaches why these particular nucleic acids and their encoded proteins have specific uses, and then goes on to demonstrate the specific uses.

For example, the specification asserts utility of the nucleic acids in expressing proteins that function as organic transporters, as actually measured by their transport activity with organic cations such as TEA, carnitine, mepyramine and quinidine. The experiments are specific to organic transporter genes and not to "any polypeptide or nucleic acid." Further, the asserted utility to design drugs that are transported by these encoded proteins is based on the observed affinity of the organic cation transporter proteins for certain types of drugs, such as actinomycin D, which are specific in their affinity for and absorbability by organic transporter proteins. The asserted utility in developing carcinostatics is based on the observed prevalence of these specific transporter proteins in tumor cells, and their ability to transport carcinostatics such as actinomycin D, etoposide, vinblastine and daunomycin. The asserted utility in gene therapy also is specific to these organic cation transporters, which, as described in the specification, are implicated in certain pathological conditions such as fatty liver, myocardiopathy, myopathy, and other conditions caused by hypocarnitemia (specification at page 16, lines 5-11). Furthermore, the asserted utility as probes to identify additional members of this organic cation transporter family is based on a detailed knowledge of their distinct, specific, sequence and structural features, as described in the specification, and the knowledge regarding sequences that are specific to organic cation transporters of this family, as described in the specification. Thus, contrary to the Examiner's assertions, the

specification is not merely asserting broad uses that could be applied to "any polypeptide or nucleic acid," but utilities that are based on specific properties of sequence, structure and function that are unique to this family of proteins and the nucleic acids encoding these proteins.

Substantial

The MPEP in discussing substantial utility at §2107.01 states that a "substantial utility" defines a "real world" use that does not require carrying out further research to identify or reasonably confirm the use. Subject matter that can have substantial utility includes research tools, such as screening assays, that are useful in analyzing compounds other than the claimed nucleic acid itself. Thus the Office is required to distinguish between subject matter that has a specifically identified, substantial utility, including as a tool to conduct further studies, from subject matter whose asserted utility requires further research to identify or reasonably confirm.

In this instance, the specification clearly meets the standard of providing a substantial utility. The specification teaches how the proteins encoded by the claimed nucleic acids can be used to study the transport of various organic cations, including carcinostatic agents, in cells, and can therefore be used to screen for compounds that are amenable to being transported by these proteins. The screening assays further find use in developing particular carcinostatic agents for different types of cancer, given the distribution of these genes in various tumor cell lines. No further research is necessary to confirm the clear identification and characterization of these genes as encoding organic cation transporter proteins; what is asserted as a utility is their use in assays to identify compounds that might be pharmacologically effective in certain diseases such as cancer (as demonstrated by the distribution of these genes and their expression in cancer tissues), or their use as probes to identify additional members of the family. Such uses as research tools more than adequately satisfy the standard of a "substantial" utility.

Applicant further wishes to point out that, contrary to the Examiner's assertion, the Brenner case has no bearing on the facts of the instant application. Brenner holds that no patent may issue for a chemical compound or a process for making such compound unless the compound is shown to have some practical utility (*i.e.*, does not require further experimentation to find a use for it or to put it into a form such that it is useful). In Brenner, the patent at issue was directed to a method of making a steroid *for which no use was*

asserted in the specification. The applicant in that case merely argued, after the fact, that it might have anti-tumor activity, based on its structural relationship to analogous compounds being tested for their anti-tumor properties. Utility was held to be lacking because the claimed methods were used to synthesize a compound that had no known or asserted utility.

In contrast, as discussed extensively above, the instant application provides nucleic acids and their encoded proteins that have an established biological function, that of an organic cation transporter, and so can be used in a variety of "real world" applications that are specific to these compounds. These "real world" applications include identifying other organic cation transporters, or screening for/developing drugs that might be more effective as carcinostatics if they show improved absorbability by these transporters (which, as the specification teaches, are expressed in several tumor cell lines). The properties of these nucleic acids and their encoded proteins are now known without question – they belong to a specific class of genes and demonstrate the functions of that class. The specification describes uses, some of which are assays to measure the transport of compounds, of the gene that correspond to its identified properties.

Credible

Applicants need assert only one credible utility to satisfy 35 U.S.C. §101, MPEP 2107.2 (see also, Raytheon v. Roper, 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 835 (1984); In re Gottlieb, 328 F.2d 1016, 1019, 140 USPQ 665, 668 (CCPA 1964)). Based on the teachings of the specification as described above, Applicants respectfully submit that the specification asserts at least one credible utility.

The USPTO has released "Guidelines for Examination of Applications for Compliance with the Utility Requirement" [guidelines, which address utility under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph] and an "Overview of Legal Precedent Governing the Utility Requirement" [legal overview] to support the guidelines.

The legal overview provided by the USPTO, in section II.B.1., explains that:

> [a]n applicant's assertion of utility creates a presumption of utility that will be sufficient, in most cases to satisfy the utility requirement of 35 U.S.C. 101. ..... To overcome this presumption, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. In other words, the Examiner must show that the asserted utility is not credible. [Emphasis added; see e.g., In re Langer 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974)].

The legal overview goes on to explain, in section II.B.2., when an asserted utility is not "credible":

> To assess credibility, the Examiner should determine if one of ordinary skill in the art would consider the assertions of the applicant to have any **reasonable scientific basis**. If they do, they should not be challenged as not being credible. Only where they do not [e.g., if the assertion is "incredible in view of contemporary knowledge"], should the Examiner challenge the statement as not being credible. (emphasis added).

Here, Applicant clearly has demonstrated a reasonable scientific basis that the asserted utilities not only are specific and substantial, but, in light of the detailed teachings regarding the structure and biological activities of this newly discovered gene family, are credible. The instant application more than amply demonstrates the useful results accomplished by the claimed nucleic acids and related vectors, cells and methods. The nucleic acids encode proteins that have been identified as organic cation transporter proteins based on their structural features, and the encoded proteins have further been shown to actually transport organic cations. The role of organic cation transporter proteins in biological systems, *e.g.*, to absorb or excrete endogenous cations, such as choline and sugars, and exogenous cations, such as a variety of drugs, was well known as of this application's effective filing date. The instant application provides another family of proteins belonging to this well known class and demonstrates their ability to function in a manner similar to other known organic cation transporter proteins. Thus, far from being an "orphan protein," for which experimentation must be carried out to determine a use, the proteins encoded by the claimed nucleic acids have an established use, namely, as transporters of organic cations in biological systems. Consequently, the nucleic acids encoding the proteins also have a credible utility, namely to produce the cation transporter proteins or express them in cells to modulate transport activity or for screening assays to identify drugs that are substrates for transport by these proteins.

Given the above credible utility, namely, that of an organic cation transporter, no further demonstration of utility is necessary. Nonetheless, the specification demonstrates that these encoded transporter proteins, which are expressed in numerous tumor cell lines, in fact do transport carcinostatic agents such as actinomycin D, etoposide, vinblastine and daunomycin. Applicant therefore has provided additional reasonable scientific basis that the nucleic acids encode proteins for specifically transporting drugs, such as carcinostatics, to various types of cancer cells. Applicant also has provided sufficient detailed characterization

of the features of this family of proteins including consensus motifs, such as a transporter motif and a nucleoside binding motif that impart the organic cation transporter function, to permit assertion of a credible use of the nucleic acids encoding these proteins as probes to isolate additional members of the family. Again, only a reasonable scientific basis is necessary to support credibility. Further, "partial success" is sufficient to demonstrate utility; it is not essential that the claimed subject matter accomplish all its intended functions or operate under all conditions (In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

In light of the above, reconsideration and withdrawal of this rejection is respectfully requested.

V. THE REJECTION OF CLAIMS 8, 10-12, 14-16, 18-21, 23-25 AND 27 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – WRITTEN DESCRIPTION

Claims 8, 10-12, 14-16, 18-21, 23-25 and 27 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description. The Examiner states that the specification adequately describes only the nucleic acid having the sequence set forth in SEQ ID NO:2 and the polypeptide having the sequence set forth in SEQ ID NO:1. It is alleged that there is inadequate written description for polynucleotide variants and fragments that (1) encode a polypeptide at least 70% identical to SEQ ID NO:1; (2) encode a polypeptide of SEQ ID NO:1, with up to 30 conservative amino acid substitutions; and (3) hybridize to SEQ ID No:2. The Examiner concludes that as of the application's effective filing date, Applicants were not in possession of the full scope of what is claimed.

This rejection is rendered moot with respect to claims 12, 14 and 15, which are cancelled herein. With respect to the remaining claims, Applicants traverse.

The written description for a claimed genus can be satisfied by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics, or a combination of such factors sufficient to demonstrate that the Applicant was in possession of the claimed subject matter. MPEP § 2163; *see* University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). It is not necessary for the application to describe each of the claim limitations exactly, but only so clearly that one of skill in the pertinent art would recognize from the disclosure that Applicant was in possession

of the claimed subject matter. Enzo Biochem. Inc. v. Gen-Probe, 296 1316, 63 1609 (Fed. Cir. 2002).

Thus, the fact that the specification does not describe or list all variants that have the recited properties is not dispositive of the written description issue. The Enzo court stated that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 'Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Further, the standard for written description is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard. It is not necessary to include in the specification that which those of skill in the art know; the specification is presumed to include all such knowledge.

The above standard is clearly met in the instant case. The claims are directed to nucleic acids (and related expression vectors, cultured cells and screening methods) encoding polypeptides that comprise or consist of the sequence of amino acids set forth in SEQ ID NO:1, or that have 76%, or at least 70%, 80% or 90% homology to the polypeptide having the amino acid sequence set forth in SEQ ID NO:1, or that hybridize under particular conditions of high stringency to the complement of SEQ ID NO:2. Dependent claims are directed to vectors and cultured cells containing these nucleic acids, and to screening methods for analyzing compounds transported by the polypeptides encoded by the nucleic acids.

The polypeptide having the amino acid sequence set forth in SEQ ID NO:1, namely, OCTN1, is extensively described and characterized in the specification. Example 2, beginning at page 21 of the specification, describes in great detail the cloning and molecular characterization of OCTN1. As Example 2 describes, the cloned human OCTN1 gene was identified as a putative organic cation transporter based on an overall homology of its encoded amino acid sequence of about 34% with the amino acid sequence of known organic cation transporters, OCT1 and OCT2. Although the overall homology was only 34%, the hydrophobicity profile of the OCTN1 sequence (Figure 1) showed a very close resemblance

to the domains of OCT1 and OCT2, including putative transmembrane regions, a consensus transporter motif, and a consensus ATP/GTP binding site motif.

The human OCTN1 protein was further used to identify other related organic cation transporter proteins: including human OCTN2 (SEQ ID NO:3), with an overall amino acid sequence homology of 76% to human OCTN1, mouse OCTN1 (SEQ ID NO:22), having an overall amino acid sequence homology of 54% to human OCTN1, and mouse OCTN2 (SEQ ID NO:27), having an overall amino acid sequence homology 50% to human OCTN1. In Example 4 of the specification, beginning at page 24, the cloning of human OCTN2 DNA, its sequence, and its structural features, including the consensus transporter motif and ATP/GTP binding site that are also present in human OCTN1, are described. Example 8, beginning at page 31, further shows that human OCTN2, like human OCTN1, has organic cation transporter activity.

Clearly, the specification describes nucleic acids encoding organic cation transporter proteins that share anywhere from 34% to 76% amino acid sequence homology with the human OCTN1 amino acid sequence, yet exhibit structural features, including transmembrane domains, a transporter motif and an ATP/GTP binding motif that characterize them as belonging to the same class of protein. The specification exemplifies several specific organic cation transporter proteins discovered herein as belonging to the human OCTN1 family, including human OCTN2 (76%, homologous to human OCTN1) mouse OCTN1 (54% homologous to human OCTN1), and mouse OCTN2 (50% homologous to human OCTN1). Based on this information, there is no question that the specification provides adequate description of the genus of nucleic acids that encode polypeptides with at least 70%, 80% or 90% identity to the protein encoded by the human OCTN1 gene, and retain the organic cation transporter activity.

Thus, there is detailed description in the specification regarding the sequence, structure and functional domains of human OCTN1, including consensus motifs defining its transporter function, such as the transmembrane domains, the transporter motif and the ATP/GTP binding motif. The specification further describes exemplary proteins of a broad range of sequence homologies (34% to 76%) to human OCTN1, all of which possess similar structure and function. Therefore, given the description of proteins having homologies from about 34% and higher that show a high degree of structural and functional similarity, there is more than adequate description to evidence possession of the isolated nucleic acids as

claimed, which encode proteins that are highly homologous (70% or above) to the hOCTN1 amino acid sequence set forth in SEQ ID NO:1, or which have one to 30 conservative amino acid substitutions (Claim 10), or which hybridize under conditions of high stringency to a nucleic acid probe that is the complement of the sequence encoding hOCTN1 (Claim 11).

With regard to Claim 11, the Examiner is also directed to the discussion in the Enzo case, which took judicial notice of the Patent Office's own Written Description Guidelines. The Enzo court, referring to Example 9 of the Synopsis of Application of Written Description Guidelines, stated "[the PTO] has determined that such claims may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." (Enzo, F.3d 1316 at 1327).

The Examiner asserts that the written description requirement for sequence variants of the isolated nucleic acid encoding hOCTN1 is not met because there is only a "recitation of percent identity" with no "identification of any particular portion of the structure that must be conserved." To the contrary, as discussed above, the specification describes the detailed characterization of hOCTN1, including specifically identifying by sequence and by secondary structure all domains of functional significance such as the transmembrane domains, the transporter motif and the ATP/GTP binding motif. The specification further describes in great detail how to prepare and identify variants that retain the function of an organic transporter (*see*, for example, page 9, line 15 to page 12, line 14). One of skill in the art would understand, given the description and specific examples of variants, and given the description in the specification and knowledge of those of skill in the art regarding function-conserving alterations, such as conservative amino acid substitutions in the functional domains (identified herein), how to alter the organic cation transporter protein hOCTN1 in a manner that retains its functional activity. The claims specify that the isolated nucleic acids encode an organic cation transporter. Thus, the claims encompass functional variants of the nucleic acid encoding hOCTN1, and the specification more than adequately describes how to identify these functional variants.

In conclusion, Applicant respectfully submits that the specification provides ample disclosure of specific, common structural features, as well as functional features, that evidence possession of the claimed isolated nucleic acids, and vectors, cells and screening methods utilizing the claimed isolated nucleic acids.

VI. REJECTION OF CLAIMS 8-25 AND 27 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 8-25 and 27 are rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate scope of enablement. In particular, the Examiner alleges that while the specification teaches that mutant proteins can be obtained by altering the amino acid sequence of the transporter protein by substitution, deletion or addition of amino acid residues to obtain functionally equivalent transporter proteins, no variant polypeptide other than the full length hOCTN1 polypeptide sequence set forth in SEQ ID NO:1 and no variant polynucleotide other than the full length hOCTN1 polynucleotide sequence set forth in SEQ ID NO:2 are actually taught. The Examiner further asserts that the specification does not teach functional or structural characteristics of the polynucleotide variants recited in the claims. The Examiner goes on to state that "function cannot be asserted from structure alone," that even single amino acid changes can significantly alter activity and/or substrate specificity, and that the Applicant has provided little or guidance beyond the "mere presentation of sequence data" to enable one of skill in the art to determine the positions in the DNA and protein that are tolerant to change.

The Examiner also states that even if the active site or binding site were identified, that "may not be sufficient" because one of skill in the art knows that the conformation assumed by a binding site is dependent on the surrounding residues and therefore substitution of non-essential residues can often destroy activity. The Examiner concludes that, in her opinion, there is a lack of guidance in the specification regarding which structural features are required to provide activity, an absence of working examples directed to the same, complexity of the claimed subject matter, unpredictability of the effects of mutation on protein structure and function, broad claims that do not recite any structural or functional limitation, and a large quantity of experimentation necessary, all of which together allegedly result in the inability to make or use the full scope of the claimed subject matter without undue experimentation.

This rejection is respectfully traversed. The rejection is rendered moot with respect to claims 12, 14 and 15, which are cancelled herein. Applicant further submits that claims 9, 13, 16, 20, 21 and new claim 36, which are directed to an isolated nucleic acid encoding the polypeptide hOCTN1 and to related cells and vectors, are outside the purview of this rejection, which is one of scope related to nucleic acids encoding variants of hOCTN1.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed.* A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

There is no requirement for disclosure of every species within a genus. Applicant is entitled to claims commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

In this instance, a consideration of the factors enumerated in *In re Wands*, including the breadth of the claims, the extensive teachings in the specification for selecting functional equivalents of the hOCTN1 organic cation transporter, the teaching of specific examples of organic cation transporter proteins belonging to the hOCTN1 family, the knowledge of those of skill in the art regarding how to make and identify functional protein variants, and the fact that identifying proteins belonging to a structurally and functionally well-characterized class is predictable given the extensive teachings of the instant application and the state of the art at the time of the effective date of the claims, leads to the conclusion that it would not require undue experimentation for one of skill in the art to make and use the subject matter as claimed.

The instant claims are directed to nucleic acids encoding polypeptides that comprise or consist of the sequence of amino acids set forth in SEQ ID NO:1, or that have 76%, or at least 70%, 80% or 90% homology to the polypeptide having the amino acid sequence set forth in SEQ ID NO:1 (*i.e.*, hOCTN1), or that hybridize with particular conditions of high stringency to the complement of the polynucleotide encoding the polypeptide having the sequence set forth in SEQ ID NO:1. The claims that specify nucleic acids encoding variants of hOCTN1 further specify that the variant is a transporter of an organic cation. Dependent claims are directed to vectors and cultured cells containing these nucleic acids, and to screening methods for analyzing compounds transported by the polypeptides encoded by the nucleic acids.

The teachings of the specification are commensurate with the full scope of the claims. The Examiner asserts that the claims directed to the variants recite no structural or functional limitations of the variants. To the contrary, the claims reciting variant sequences all specify that the isolated nucleic acid encodes a polypeptide that is a transporter of an organic cation. The specification provides extensive teachings regarding the structure of hOCTN1, including its functional domains, how to alter the nucleic acid encoding hOCTN1 in a manner that produces variants that retain the transporter function, the identification of naturally-occurring variants that belong to the hOCTN1 family, how to test the transport activity of the variants, and how to screen for compounds that have an affinity for the transporter proteins.

As discussed above in addressing the written description rejection, Example 2, beginning at page 21 of the specification, describes in great detail the cloning and molecular characterization of OCTN1. As taught in Example 2 and in Figure 3, every functional domain of hOCTN1 has been identified by its sequence and its function, including transmembrane domains, a consensus transporter motif and a consensus ATP/GTP binding motif. Given this detailed characterization and the teachings in the specification on how to select for and identify a protein having transporter function (*see*, for example, page 9, line 15, to page 12, line 14), it would take no more than routine experimentation to screen for variants of the hOCTN1 encoding nucleic acid that encode organic cation transporter proteins.

The specification also provides no less than three other specific examples of organic cation transporter proteins, all with different degrees of homology to hOCTN1, which were discovered as belonging to the hOCTN1 family. In Example 4 of the specification, beginning at page 24, the cloning of human OCTN2 (hOCTN2) cDNA, whose encoded protein is 76% homologous to hOCTN1, its sequence, and its structural features, including the consensus transporter motif and ATP/GTP binding site that are also present in human OCTN1, are taught. Example 8, beginning at page 31, further shows that human OCTN2, like human OCTN1, has organic cation transporter activity. The sequence of the hOCTN2 polypeptide is set forth in SEQ ID NO:3, and the corresponding polynucleotide sequence is set forth in SEQ ID NO:4. In Example 9, beginning at page 33, the cloning and sequencing of mouse OCTN1 cDNA, whose encoded protein is 54% homologous to the hOCTN1 polypeptide, is described. The sequence of the mouse OCTN1 polypeptide is set forth in SEQ ID NO:22, and the corresponding polynucleotide sequence is set forth in SEQ ID NO:23. In Example 10, beginning at page 34, the cloning and sequencing of mouse OCTN2 cDNA, whose encoded

protein is 50% homologous to the hOCTN1 polypeptide, is described. The sequence of the mouse OCTN1 polypeptide is set forth in SEQ ID NO:27, and the corresponding polynucleotide sequence is set forth in SEQ ID NO:28.

Examples 6-8 further teach how to measure the organic cation transporter function of these proteins. Clearly, the extensive teachings of the specification regarding the sequence and structure (hydrophobicity plot, *e.g.*, see Figure 1) of the functional domains of hOCTN1, how to produce and select for functional equivalents of hOCTN1, how to measure their transport activity, and the actual exemplification of such variants, when combined with the additional advanced knowledge of those of skill in the art regarding conservative amino acid substitutions and other alterations that conserve structure and/or function, would allow one of skill in the art to identify variants as claimed with no more than routine experimentation.

The Examiner cites numerous publications that allegedly evidence "unpredictability" of the relationship between sequence and/or structure variation, and function. In that context, she alleges that it is unpredictable which of the variants produced as taught by the specification will actually retain cation transporter activity. In response, Applicant respectfully submits that this is not the proper standard for enablement. To satisfy the requirement of enablement, a claim does not have to explicitly exclude every conceivable inactive variant. ("[I]t is not a function of the claims to specifically exclude either possible inoperative substances or ineffective reacting proportions". In Application of Dinh-Nguyen, 492 F.2d 865 at 858-9 181 USPQ 46 (CCPA (1974)). Rather, the question is whether by following the teachings of the application, one of skill in the art can practice what is claimed with perhaps routine, but not undue, experimentation. In this instance, given the extensive teachings of the specification regarding (1) the structure of hOCTN1 (and another protein in the family, hOCTN2), including the sequence and structure of each of its functional domains; (2) how to systematically alter the amino acid sequence of hOCTN1 to obtain variants and/or obtain nucleic acid variants by hybridization techniques; (3) how to test the variants for organic cation transporter activity; and (4) obtaining actual variants of hOCTN1 that do possess organic cation transporter activity (hOCTN2), combined with the knowledge of those of skill in the art regarding these techniques, Applicant submits that one could, by following the teachings of the application, readily obtain variants that encode organic cation transporter proteins commensurate with the full scope of the subject matter as claimed. There is certainly less unpredictability involved here than in the In re Wands case, which involved

making and testing antibodies, not one of which could be predicted to meet the claimed criteria until it was actually tested. The Court in that case found that the amount of experimentation was not undue.

Moreover, while it may be true that in some instances a single amino acid substitution can affect the function of a polypeptide, it is also recognized in the art that, for any given protein, many residues can be substituted without affecting a specified function. Given the detailed knowledge of sequence, structure and function of a protein, one can predictably alter its sequence in a manner that retains function. This much is exemplified by Applicants' own disclosure of SEQ ID NOS:1 and 3 (*see* discussion of hOCTN1 and hOCTN2 above), and by the prior art. *See, e.g.*, Bowie *et al.* (1990) *Science* 247:1306-1310 (copy enclosed). At page 1306, lines 12-13, Bowie teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie *et al.* cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably, the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on Bowie *et al.*'s teachings, to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity. These are far better odds than those at issue in In re Wands, in which the court said that screening many hybridomas to find the few that fell within the claims was not undue experimentation. The question is not whether it is possible to abolish activity with a point mutation (as the Examiner seems to believe), but rather whether one of ordinary skill can produce, without undue experimentation, mutants in which the activity is not abolished. Based on Bowie *et al.*'s teachings, one would predict that even random substitution of residues in SEQ ID NO:1 will predictably result in a majority of the variants having full or partial transporter activity.

In sum, the fact that it may be theoretically possible to make a variant that lacks function seems irrelevant to the question of whether one of ordinary skill in the art would know how to make and use variants of the claimed nucleic acids whose encoded polypeptides retain function, without undue experimentation. The Examiner has provided no evidence that one of skill in the art could not use the guidance provided in the specification to predict and determine, by routine testing, what amino acids could be changed without affecting cation

transporter function. Given the specific limitations recited in the claims, the high level of skill in the art, the detailed guidance provided by Applicants, the disclosure of working examples, and the routine nature of any experimentation that might be required to make and use the claimed nucleic acids and related vectors, cells and screening methods, the present claims are clearly enabled.

VII. REJECTION OF CLAIMS 8-25 and 27 UNDER 35 U.S.C. §102(a)

Claims 8-25 and 27 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Tamai *et al.* (*FEBS Lett.* 419: 107-111 (1997)) because, according to the Examiner, Tamai *et al.* discloses an OCTN1 DNA sequence that is 100% identical to SEQ ID NO:2 of the instant application, its structural features and sequence motifs, the cloning of OCTN1 cDNA into expression vectors, transfection of the resulting expression vectors into cells, culturing the cells and measuring the transport of various compounds in the cultured cells. The Examiner asserts that Applicant cannot rely on the foreign priority papers to overcome this rejection because English translations of the papers have not been made of record in accordance with 37 C.F.R. § 1.55.

This rejection is rendered moot with respect to Claims 12, 14 and 15, which are cancelled herein. With respect to the remaining claims, this rejection is respectfully traversed. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

First, in compliance with the requirements of 37 C.F.R. § 1.55, Applicants have enclosed with this response (*see* Appendix attached hereto) certified English translations of the following two priority documents of the instant application:

1) Japanese application JP 9-260972, titled "Transporter Genes," filed September 8, 1997; and

2) Japanese application JP 10-156660, titled "Transporter Genes," filed May 20, 1998.

Applicant respectfully submits that at least with respect to Claims 8, 9, 11, 13, 16-27, 29, 30 and 32-36, Tamai *et al.*, which has a publication date of December 1997, is not prior art because the claims find basis in priority document 1) above, filed September 8, 1997. With respect to the remaining claims (Claim 10 and new Claim 31), even if Tamai *et al.* could qualify as prior art as the "work of others" under 35 U.S.C. § 102(a) (an assertion

Applicants do not concede), the rejection fails because claim 10 as amended and new claim 31 are not anticipated by Tamai *et al.*

Claim 10 as amended herein is directed to an isolated nucleic acid encoding a polypeptide with one to 30 conservative amino acid substitutions relative to the amino acid sequence set forth in SEQ ID NO:1. Claim 31 is directed to the nucleic acid of claim 8 whose encoded polypeptide is 76% homologous to the amino acid sequence set forth in SEQ ID NO:1. Tamai *et al.* does not disclose a nucleic acid whose encoded polypeptide has any amino acid substitutions, conservative or otherwise, relative to the OCTN1 amino acid sequence set forth in SEQ ID NO:1 (limitation of Claim 10), nor nucleic acids encoding a polypeptide whose sequence is 76% homologous to the amino acid sequence set forth in SEQ ID NO:1 (limitation of Claim 31). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990). Therefore, because Tamai *et al.* does not disclose every element of Claims 10 and 31, Tamai *et al.* does not anticipate these claims, nor any claims that depend therefrom.

In light of the above, reconsideration and withdrawal of this rejection is respectfully requested.

VIII. REJECTION OF CLAIM 11 UNDER 35 U.S.C. §102(b)

Claim 11 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Martin *et al.* (Genbank Accession No. HSL81760, April 9, 1997) because Martin *et al.* discloses an isolated nucleic acid sequence that the Examiner maintains would hybridize to nucleotides 1-539 of the sequence set forth in SEQ ID NO:2. The Examiner states that Claim 11 has been interpreted as "encompassing an infinite number of nucleic acids" that hybridize to the nucleic acid sequence of SEQ ID NO:2 because DNA will hybridize under conditions of low or no stringency." This rejection is respectfully traversed. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Applicant respectfully disagrees that the recitation in Claim 11 of hybridizing under "stringent conditions" encompasses conditions of "low or no stringency." Nonetheless, in the interest of advancing prosecution of this application, Claim 11 is amended herein to specify particular hybridization conditions of high stringency, and to further specify that the nucleic acid encodes a transporter of an organic cation.

Martin *et al.* discloses the sequence of a cDNA clone derived from human chromosome 5q. The reference merely discloses part of the sequence of chromosome 5q in the Genbank database; no gene and/or function is attributed to the cloned molecule. Of the 3081 base sequence disclosed in Martin *et al.*, the portion of the sequence beginning at base 1708 and ending at base 1170 is complementary to the sequence beginning at base 1 and ending at base 539 of SEQ ID NO:2. This corresponds to about 25% of the entire sequence (2135 bases) of SEQ ID NO:2. The polypeptide encoded by bases 1-539 of SEQ ID NO:2 is 131 amino acids long, which is less than 25% of the full length protein (551 amino acids, *see* SEQ ID NO:1) encoded by the nucleic acid whose sequence is set forth SEQ ID NO:2.

There is no disclosure in Martin *et al.* that would suggest that the nucleic acid encodes a protein having an organic cation transporter function as recited in claim 11. The portion of the nucleic acid sequence disclosed in Martin *et al.* that encodes part (amino acids 1-131 of SEQ ID NO:1, which is less than 25% of the 551amino acid sequence) of the protein encoded by the nucleic acid of SEQ ID NO:2, even if expressed, would not contain the sequences corresponding to motifs that are responsible for key functional characteristics of the organic cation transporter encoded by SEQ ID NO:2, such as the transporter motif (amino acids 160-175 of SEQ ID NO:1) and the nucleoside binding motif (amino acids 218-225 of SEQ ID NO:1).

Because Martin *et al.* does not disclose a nucleic acid encoding a polypeptide having an organic cation transporter activity as recited in Claim 11, therefore Martin *et al.* does not anticipate the claim.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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